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16. ABSTRACT

To improve aerosol therapy regimens or to assess the health hazards of inhaled toxic particulates, the dose delivered to the human respiratory tract must be determined. The efficiency with which an aerosol is deposited in various compartments of the tract is a function of its mass median aerodynamic diameter, MMAD (Task Group on Lung Dynamics, 1966). If an airborne particle is hygroscopic, it will change in geometric diameter and density as a result of water vapor uptake; its MMAD, therefore, will vary with location throughout the human respiratory tract. As a result, its dose distribution will differ from that for a nonhygroscopic (i.e., hydrophobic) aerosol of identical inhaled MMAD.

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THE EFFECT OF HYGROSCOPIC GROWTH UPON THE REGIONAL DISPERSION OF PARTICULATES IN HUMAN AIRWAYS

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INTRODUCTION

The success of an aerosol therapy protocol is contingent upon a proper quantity of drug being delivered to an appropriate site within the respiratory tract to elicit a therapeutic effect. Likewise, an accurate risk assessment of the threat to human health presented by airborne pollutants requires knowledge of their locations of deposition among airways. An identification of those factors which influence the behavior and fate of inhaled particulates, therefore, is important for both the introduction of medicinal agents into the body via the inhalation route and the hazard evaluation of ambient toxicants.

For aerosols consisting of hydrophobic (i.e, not having an affinity for the uptake of water vapor) particulates, the Task Group on Lung Dynamics (1966) and Lippmann (1977) have illustrated that deposition efficiencies within the tracheobronchial (TB) and pulmonary (P) compartments of the human respiratory tract may be expressed as functions of the mass median aerodynamic diameters (MMADs) of their particulate size distributions. The variance in deposition for a given MMAD can be related to the geometric standard deviations (σ_g) of the latter.

Since the TB and P compartments have particulate clearance mechanisms which differ in mode of action, effectiveness, and rate, it is important to know the intercompartmental distribution of the total dose delivered to

the lung. It allows the relative dose delivered to different airway cells to be accounted for following inhalation exposures to medicines or contaminants.

Many therapeutic drugs and air pollutants are hygroscopic in character (i.e, will readily take up and retain moisture). In the humid atmosphere of the respiratory tract, such particulates will have varying densities and sizes and, therefore, different regional dispersion patterns than those anticipated if they were hydrophobic. It is the purpose of this work to study the effects of hygroscopicity upon the regional disposition of certain bronchodilator aerosols dispensed from hand-held metered-dose devices, and a class of the ambient sulfate aerosols, ammonium bisulfate (NH_4HSO_4).

METHODS

A mathematical model has been developed which simulates the behavior of particulates within the human respiratory tract. It can be used to calculate the deposition probabilities within the extrathoracic (ET), TB, and P compartments during inspiration, pause, and expiration. ET airways consist of the oro- and nasopharyngeal regions, and larynx. Certain features of the model are outlined below.

Airway Morphology

A variety of anatomical geometries--symmetric and asymmetric--have been proposed as being acceptable structural descriptions of the TB and P compartments of the lung; for examples, Weibel (1963) and Horsfield *et al*. (1971). We have chosen to use the symmetric, dichotomously branching Model A architecture proposed by Weibel (1963) with airway lengths and diameters as recommended by Soong *et al*. (1979). An earlier work (Martonen, 1983a) has shown that a symmetric

airway system is suitable for deposition modeling purposes.

Airway Flow Patterns

Pedley *et al.* (1979) have reviewed numerous *in vitro* and *in vivo* studies of respiratory tract gas dynamics, and discussed the complexities of air motion. Here, we shall comment only on the most salient features. In upper airways, unstable air flow patterns are produced by the focused stream entering the trachea from the narrow glottis aperature of the larynx (i.e., a laryngeal jet), and further induced by surface irregularities (including cartilaginous rings and carinal corrugations) and the very branching nature of the TB tree itself. The depth to which the instabilities penetrate *in vivo* airways is not known, but, as noted by Martonen (1982) unstable flow patterns exist at locations where Reynolds numbers would predict laminar conditions within smooth, straight tubes. Moreover, even when flows are stable and laminar, their profiles are skew-shaped. Also, double-vortex, secondary-flow currents have been measured normal to the aforementioned primary flows. In this work, we shall assume the transitory unstable-to-laminar flow patterns used by Martonen (1982) in an attempt to be physiologically realistic.

Particulate Deposition Probability Equations

For the ET airways, the system of empirical formulas derived by Martonen (1983b) will be used to compute particulate losses. In the distal TB and P compartments, deposition will be assumed to occur by the simultaneous action of the inertial impaction, sedimentation and diffusion (Brownian motion) mechanisms. A series of equations has been proposed by Martonen (1982) for use in simulating particulate behavior in the unstable and skewed laminar air flow patterns previously discussed. The accuracy with which the equations

predict particulate deposition efficiencies in the TB and P airways has been established by comparisons of theoretically predicted deposition patterns with experimental data from inhalation exposures conducted with human test subjects (Martonen, 1983a,b); hence, they will be utilized here.

Breathing Mode

Tests quantitating TB and P deposition are routinely conducted using mouth, rather than nose, breathing. Key parameters characterizing a breathing pattern are its tidal volume (ml) and frequency (breaths/min). The general stylized pattern used in this model is illustrated in Figure 1; it consists of constant (but unequal) inspiratory and expiratory flow rates, with intermittent pauses, and has been shown (Martonen, 1983b) to be suitable for the spontaneous breathing regimens used in tests done at the Institute of Environmental Medicine, New York University (Chan and Lippmann, 1980).

When the fate of hygroscopic aerosols is being investigated, there are additional factors which must be considered. Two of the most important are noted briefly below.

Particulate Hygroscopicity

The hygroscopic behavior of airborne particulates is a function of material properties per se, and size. The latter dependency is termed the Kelvin Effect (Friedlander, 1977). Tang (1976), Tang et al. (1977) and Tang and Munkelwitz (1977) have theoretically studied the growths of several sulfate aerosols of health effects concern and have experimentally measured the final equilibrium sizes achieved by NH_4HSO_4 particulates in certain temperature (T) and relative humidity (RH) environments. Martonen et al. (1982) and Martonen and Lowe (1984) have measured the growth rates of two bronchodilator aerosols within a surrogate model of the upper TB tree. The data are given in Figure 2. The drugs both contain isoproterenol

hydrochloride as the active medicinal agent, and the same buffering substances; they differ in that the 0.5% Isuprel® solution contains glycerin. It is apparent that the presence of glycerin retards growth. Possible mechanisms for the inhibition have been discussed (Bell and Ho, 1981).

Airway Environment

Because of the air conditioning role of the ET airways, the T and RH of the distal TB and P compartments will be different for air inhaled through the nose or mouth. To simulate mouth breathing inhalation exposure tests, Martonen and Miller (1984) assumed a T of 37°C within all TB and P airways, with a changing RH profile. For the latter, we also will assume that the trachea's RH is 90% and that the RH will go up by 1% in each succeeding generation until a RH of 99% is achieved in generation 10 (using Weibel's (1963) terminology); all distal airways will have a RH of 99.5%. Such a monotonically increasing RH profile is consistent with published laboratory measurements of *in vivo* atmospheres (Martonen *et al.*, 1985).

Founded upon the predictions of a computer model, the occurrence of a transient supersaturation (e.g., RH > 100%) condition in the upper TB airways during inspiration has been suggested by Ferron *et al.* (1983, 1985). But, these predictions are in conflict with data from experimental studies--for examples, Ingelstedt (1956) and Ingelstedt and Toremalm (1960)--perhaps because of the questionable nature of several of the assumptions made in the theoretical description and formulation of heat and mass transfer phenomena taking place in the bronchi. Several counterarguments to the feasibility of supersaturation actually occurring *in vivo* under realistic (ambient and physiologic) conditions have been raised by Martonen and Miller (1984), Martonen *et al.* (1985) and Martonen and Graham (in press).

To compute the effects of hygroscopicity upon deposition, the growth data were incorporated into the aerosol deposition model as computer subroutines describing changes in particulate size and density as a function of location within the respiratory tract. For NH_4HSO_4 particulates, where only the final sizes attained at given RHs are known, computations were done using the format of Martonen and Clark (1983). For the bronchodilator aerosols, where growth as a function of time was measured, computations were done in the manner of Martonen (1982).

RESULTS AND DISCUSSION

In Figures 3-5 our calculated regional dispersion patterns for hydrophobic Fe_2O_3 aerosols deposited within the TB and P compartments of the lung are compared to the experimental data of Chan and Lippmann (1980). The model accurately predicts deposition probabilities over a wide range of particulate diameters, ≅0.2 μm D_g (geometric) to ≅8 μm D_{ae} (aerodynamic), indicating that aerosol dynamics is being properly modeled. The theoretical deposition curves, having been validated by the laboratory findings, will be used here as "controls" to study hygroscopic growth effects.

Chemical analyses of cascade impactor samples of ambient urban air taken by Patterson and Wagman (1977) have indicated that sulfate and ammonium ions are mostly extracted from particulates with MMADs between 0.2-0.6 μm. However, Israel *et al.* (1983) have detected "sulfate clouds" with pronounced mass distribution peaks in the 1-5 μm MMAD size range. The predicted influence of hygroscopicity upon the regional dispersion of such-sized ambient pollutant NH_4HSO_4 aerosols within the lung is shown in Figures 3 and 4. In the TB tree there appears to be a critical size of ≅ 0.5 μm D_g. For larger particulates, computer results show that water vapor uptake increases

deposition due to increased effectiveness of the sedimentation and/or inertial impaction mechanisms. Growth effects can be substantial: for D_{ae} = 4 μm deposition is enhanced by a factor of 3, from ≅ 30% to ≅ 90%. For particulates smaller than 0.5 μm the effect of growth is to decrease deposition because of the reduced effectiveness of the diffusion mechanism; a comparable submicron critical size can be observed in the P compartment. For hydrophobic particulates, deposition in the P airways is maximum, ≅ 40%, when D_{ae}≅ 4 μm. NH_4HSO_4 particulates of such size, however, are deposited mostly in the TB tree, and P deposition peaks at a size of ≅1.3 μm.

The aerosols produced by several kinds of metered-dose, hand-held devices have been characterized by Hiller et al. (1978); MMADs ranged from approximately 2.8 - 4.3 μm. The micronized powder form of isoproterenol hydrochloride had a MMAD = 2.8 μm with a σ_g = 1.8. Since the active agent is a β-adrenergic stimulator it will be beneficial to maximize TB deposition if the drug is to be administered via the inhalation route rather than ingestion. In Figure 5, the effects of hygroscopic growth upon the relative distribution of such bronchodilator aerosols are illustrated. Growth enhances the deposition of 1% Isuprel® aerosols by up to 50% relative to the like-sized hydrophobic aerosols over the relevant size range of 1 μm $\leq D_{ae} \leq$ 5 μm. For 0.5% Isuprel® aerosols, however, hygroscopic effects are negligible because of reduced particulate growth rates caused by the presence of glycerin in the diluted drug solution.

The effect of the growth-inhibiting role of glycerin upon the regional dispersion of inhaled particulates raises an interesting question. Namely, would it be possible to add humectants to drugs administered by inhalation

so as to control their growth--and thereby their sites of deposition--and enhance the efficacies of aerosol therapy protocols?

The data presented in Figures 3-5 indicate that growth can have a substantial influence on the disposition of inhaled particulates within the lung. Since the toxic or therapeutic dose delivered to airway cells depends upon duration of exposure, and different regions of the respiratory tract have clearance mechanisms that vary in effectiveness and rate, it is apparent that hygroscopicity must be accounted for to ensure the accurate hazard evaluation of airborne contaminants and to optimize applications of aerosol therapy.

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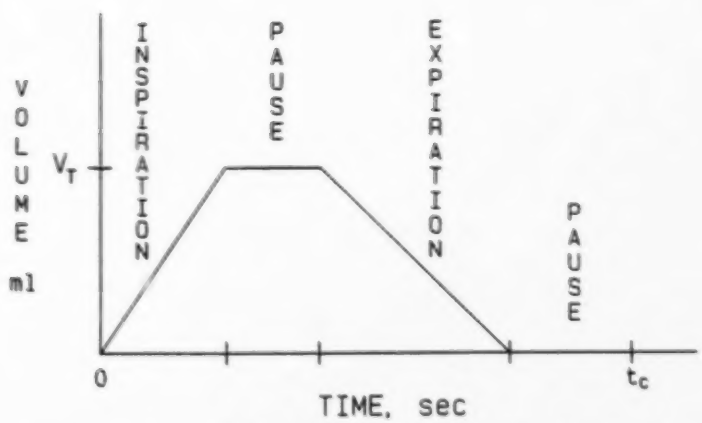

Figure 1. A general breathing pattern for a stylized time cycle t_c for use in aerosol deposition and gas mixing (Martonen and Wilson, 1982) models. V_T is tidal volume.

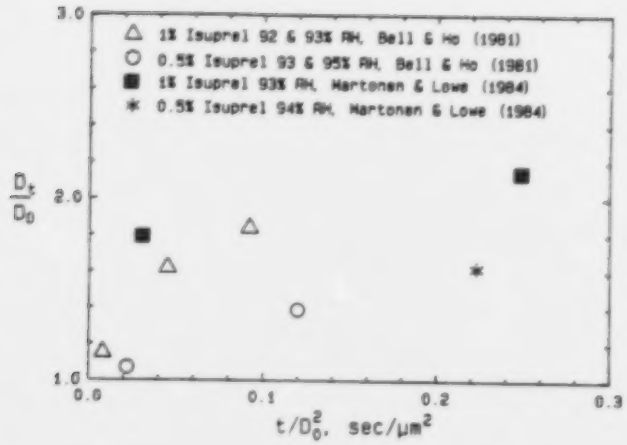

Figure 2. Hygroscopic growth rate measurements of bronchodilator aerosols within the environment of a laboratory model of human bronchial airways.

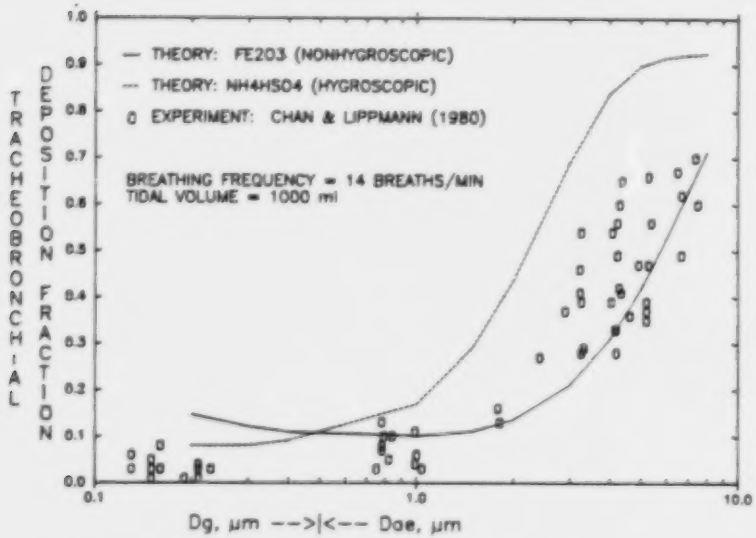

Figure 3. The influence of hygroscopic growth upon tracheobronchial deposition of ammonium bisulfate aerosol during spontaneous mouth breathing maneuvers (normalized to aerosol mass entering the trachea). Dg and Dae represent particulate geometric and aerodynamic diameters, respectively.

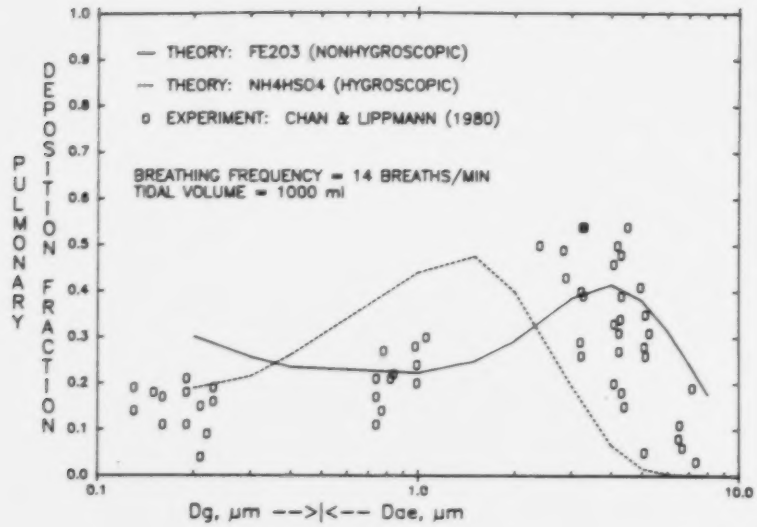
— THEORY: FE2O3 (NONHYGROSCOPIC)
-- THEORY: NH4HSO4 (HYGROSCOPIC)
o EXPERIMENT: CHAN & LIPPMANN (1980)
BREATHING FREQUENCY = 14 BREATHS/MIN
TIDAL VOLUME = 1000 ml
PULMONARY DEPOSITION FRACTION
Dg, μm -->|<-- Dae, μm

Figure 4. The influence of hygroscopic growth upon pulmonary deposition of ammonium bisulfate aerosol during spontaneous mouth breathing maneuvers (normalized to aerosol mass entering the trachea). Dg and Dae represent particulate geometric and aerodynamic diameters, respectively.

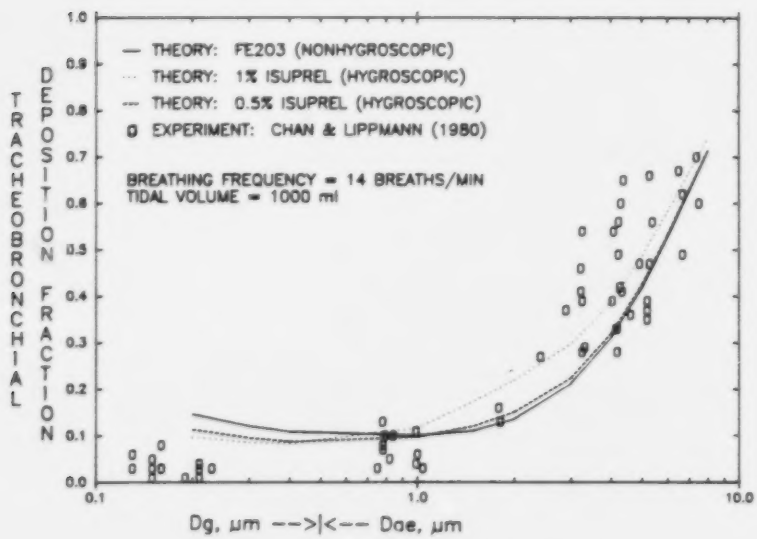
— THEORY: FE2O3 (NONHYGROSCOPIC)
··· THEORY: 1% ISUPREL (HYGROSCOPIC)
-- THEORY: 0.5% ISUPREL (HYGROSCOPIC)
o EXPERIMENT: CHAN & LIPPMANN (1980)
BREATHING FREQUENCY = 14 BREATHS/MIN
TIDAL VOLUME = 1000 ml
TRACHEOBRONCHIAL DEPOSITION FRACTION
Dg, μm -->|<-- Dae, μm

Figure 5. The influence of hygroscopic growth upon tracheobronchial deposition of bronchodilator aerosol during spontaneous mouth breathing maneuvers (normalized to aerosol mass entering the trachea). Dg and Dae represent particulate geometric and aerodynamic diameters, respectively.

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